

I. AMENDMENTS TO THE CLAIMS:

1. (Currently Amended) A process for the manufacture of NO-donating compounds comprising;

(1),



(I)

(II)

using an acidic or dehydrating agent and a first solvent, optionally followed by purification using extraction or crystallization, and

(2),

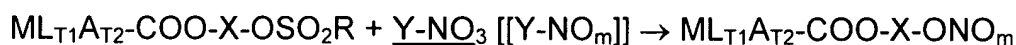


(II)

(III)

using a second solvent, a base and optionally a catalyst, followed by purification ~~using extraction and crystallization~~, and

(3),



(III)

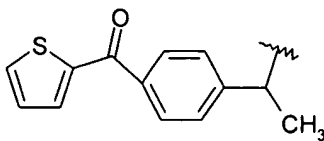
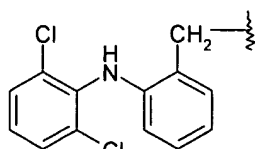
(IV)

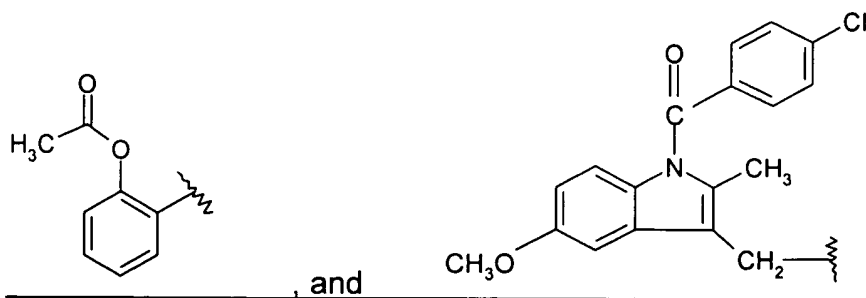
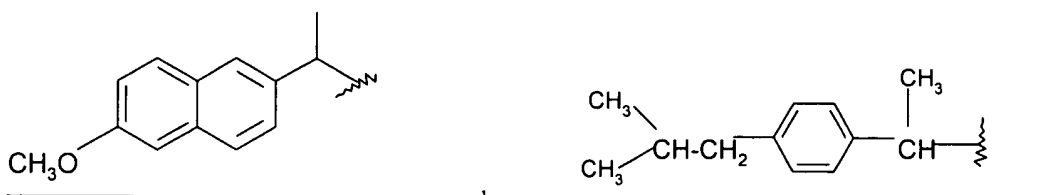
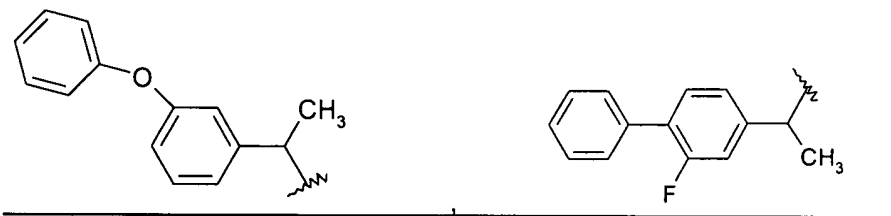
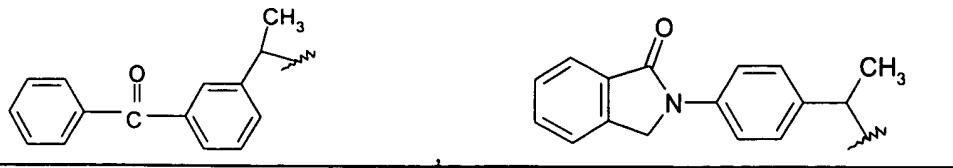
using a third solvent, at a maximum reaction temperature of 90°C, and optionally a catalyst,

optionally followed by a crystallization process for obtaining the compound of formula IV in a substantially crystalline form, and

wherein:

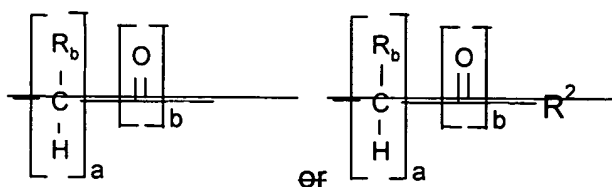
ML_{T1}A_{T2} is selected from the group consisting of:





M is a radical of a physiologically active compound;

L is O, S, (CO)O, (CO)NH, (CO)NR¹, NH, NR¹, wherein R¹ is a linear or branched alkyl group, or



wherein R_b is H, C_{1-12} -alkyl or C_{2-12} -alkenyl;

R^2 is $(CO)NH$, $(CO)NR^1$, $(CO)O$, or CR^1 and a and b are independently 0 or 1;

A is a substituted or unsubstituted straight or branched alkyl chain;

X is selected from the group consisting of: linear $-(CH_2)_{w1}-$, wherein $w1$ is an integer of from 2 to 10; $-(CH_2)_{w2}-O-(CH_2)_{w3}-$, wherein $w2$ and $w3$ are integers of from 2 to 10; or $-(CH_2-CH_2-O)_2-CH_2-CH_2-$ a carbon linker ;

R is selected from the group consisting of C_1 - C_8 alkyl, ~~phenyl, phenylmethyl,~~

C_4 - C_6 -alkylphenyl, halophenyl, nitrophenyl, acetaminophenyl, halogen, CF_3 and ~~n - C_4F_9 ;~~

$Y-NO_3$ is selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zinc nitrate and tetraalkylammonium nitrate, wherein alkyl is a straight or branched C_1 - C_{18} -alkyl, and a mixture thereof;

m is ~~[[1 or]]~~ 2; and

$T1$ and $T2$ are each independently 0, 1, 2 or 3;

with the proviso that when $ML_{T1}A_{T2}-COOH$ is naproxen, then X is not $(CH_2)_4$.

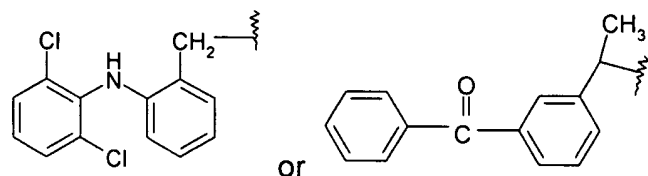
2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Canceled)

6. (Currently Amended) The process according to claim 1 [[5]], wherein the group $ML_{T1}A_{T2}$ is:



7. (Previously Presented) The process according to claim 1, wherein the crystallization process for the compound of formula IV comprises:

- a) i) dissolving the compound in a fourth solvent;
or,
ii) extracting the compound from the reaction solution into a fourth solvent;
or,
iii) starting from the reaction solution comprising the compound;
- b) evaporating the fourth solvent;
- c) adding an anti-solvent and/or cooling
- d) isolating the crystals formed, and optionally;
- e) recrystallizing the crystals formed or isolated.

8. (Currently Amended) The process according to claim 7, wherein the crystallization process for compound 2-[2-(nitrooxy)-ethoxy]ethyl{2-[(2,6-dichlorophenyl)amino]phenyl}acetate (IVa) comprises:

- a) ~~iii) starting from the reaction solution comprising the compound~~ extracting the compound from the reaction solution into the fourth solvent;
- b) evaporating the fourth solvent;
- c) ~~adding an anti-solvent and/or~~ isopropanol and cooling the resulting solution;
and
- d) isolating the crystals formed ~~and optionally;~~
- e) ~~recrystallizing the crystals formed or isolated .~~

9. (Previously Presented) The process according to claim 1, wherein the acidic or dehydrating agent is selected from the group consisting of sulphuric acid or its salts, perchloric acid polystyrene sulphonic acids, zeolites, acidic clays, sand in combination with strong hydrophilic acids, and montmorillonites.
10. (Previously Presented) The process according to claim 1, wherein the first solvent is a non-polar and/or non acidic solvent.
11. (Previously Presented) The process according to claim 1, wherein the second solvent is selected from a group consisting of toluene, cumene, xylenes, ethyl acetate, acetonitrile, butyl acetate, and isopropyl acetate.
12. (Previously Presented) The process according to claim 1, wherein the base is triethylamine or *N*-methyldmorpholine.
13. (Previously Presented) The process according to claim 1, wherein the catalyst is 4-(dimethylamino)pyridine.
14. (Previously Presented) The process according claim 1, wherein the compound of formula III is crystallized from an organic solvent.
15. (Previously Presented) The process according to claim 14, wherein an anti-solvent is used in the crystallization of compound of formula III.
16. (Previously Presented) The process according to claim 1, wherein $Y-NO_3$ is selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, and mixtures thereof.
17. (Currently Amended) The process according to claim 1, wherein the third organic solvent is selected from the group consisting of *N*-methylpyrrolidinone,

sulpholane, tetramethylurea, 1,3-dimethyl-2-imidazolidinone, acetonitrile, methyl isobutylketone, ethyl acetate, butyl acetate, isopropyl acetate, and mixtures thereof.

18. (Previously Presented) The process according to claim 1, wherein the phase transfer-catalyst is selected from the group consisting of tetraalkylammonium salt, arylalkylammonium salt, tetraalkylphosphonium salt, arylalkylphosphonium salt, crown ether, pentaethylene glycol, hexaethylene glycol, polyethylene glycols, and mixtures thereof.

19. (Previously Presented) The process according to claim 7, wherein the fourth solvent is selected from the group consisting of lower alkyl acetates, lower alkyl alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, heteroaromatic hydrocarbons, dialkyl ketones, dialkyl ethers, nitriles, water, and mixtures thereof.

20. (Previously Presented) The process according to claim 7, wherein the anti-solvent is selected from the group consisting of ethanol, 2-propanol, toluene, cumene, xylenes, ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes, cyclohexanes, cycloheptanes, and mixtures thereof.

21. (Previously Presented) The process according to claim 7, wherein the solvent in step d) is selected from the group consisting of toluene, cumene, xylenes, methyl *iso*-butyl ketone, di-*n*-butyl ether, *tert*-butyl methyl ether, tetrahydrofuran, acetonitrile, *n*-butyl acetate, dichloromethane, and mixtures thereof.

22. (Currently Amended) The process according to claim 1, wherein the process is conducted at a temperature ~~between 40°C and 120°C~~ below 130°C in (1) and (2).

23. (Canceled)

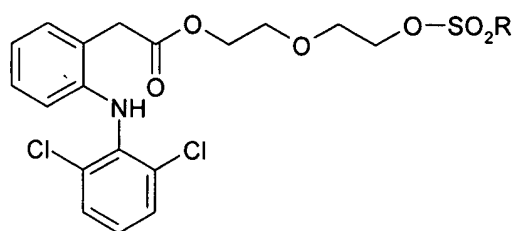
24. (Previously Presented) The process according to claim 1, wherein the chemical purity of Form A of compound IVa is above 95%.

25. (Canceled)

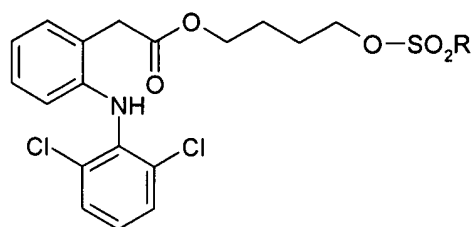
26. (Currently Amended) The process according to claim [[25]] 49, wherein the compound of formula IVd is the S-enantiomer of NO donating ketoprofen.

27-31. (Canceled)

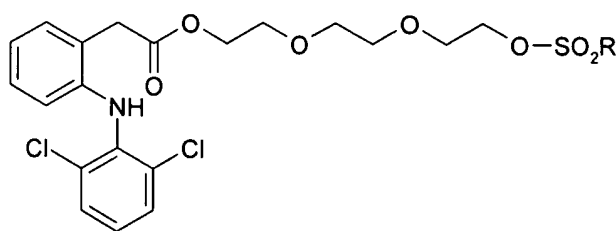
32. (Currently Amended) Compounds of formula IIIa, IIIb, IIIc and IIId:



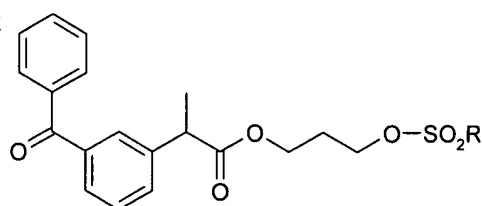
IIIa



IIIb



IIIc



IIId

wherein R is selected from the group consisting of C₁-C₈ alkyl, ~~phenyl, phenylmethyl,~~
C₁-C₄-alkylphenyl, ~~halophenyl, nitrophenyl, acetaminophenyl, halogen, CF₃, and~~
~~n-C₄F₉.~~

33. (Canceled)

34. (Currently Amended) A method for manufacturing a pharmaceutically active compound comprising providing Use of the compounds of formula III, $ML_{T1}A_{T2}-X-O-SO_2R$, wherein M, L, A, T1, T2, X and R are as defined in claim 1, and manufacturing a pharmaceutically active compound from the compounds of formula III as an intermediate for the manufacturing of a pharmaceutically active compound.

35. (Currently Amended) A method for preparing a medicament for the treatment of pain and/or inflammation comprising providing Use of intermediate compounds of formula IIIa, IIIb, IIIc and IIId as defined in claim 32, prepared according to the process described under step 1 and 2 of claim 1, for the manufacturing of a medicament a pharmaceutically active compound from the compounds of formula IIIa, IIIb, IIIc and IIId, and combining the pharmaceutically active compound with one or more diluents, excipient or carriers for the treatment of pain and/or inflammation.

36-38. (Canceled)

39. (New) The process according to claim 1, wherein R is $-CH_3$.

40. (New) A process according to claim 1, wherein Y- NO_3 of step (3) is sodium nitrate and tetrabutylammonium nitrate, the third solvent is acetonitrile, and step (3) is conducted at a temperature of $87^\circ C$.

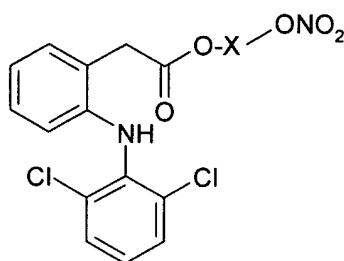
41. (New) A process according to claim 1, wherein Y- NO_3 of (3) is sodium nitrate and tetrabutylammonium nitrate, the third solvent is a mixture of n-butyl acetate and water, and step (3) is conducted at a temperature of $90^\circ C$.

42. (New) The process according to claim 1, wherein w1 is 3 or 4, and w2 and w3 are 2.

43. (New) The process according to claim 11, wherein the second solvent is selected from a group consisting of toluene, cumene, and xylenes.

44. (New) The process according to claim 12, wherein RSO_2Cl is methanesulfonyl chloride and the base is *N*-methyldmorpholine.

45. (New) A process according to claim 1 for the manufacture of the compound of formula IVa

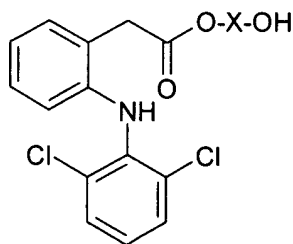


IVa

wherein $\text{X} = -\text{C}_2\text{H}_4\text{OC}_2\text{H}_4-$,

comprising:

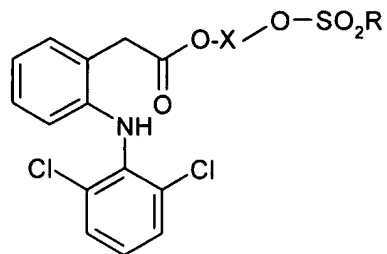
(1) reacting diclofenac with diethylenglycol and concentrated sulphuric acid in toluene to obtain the compound of formula IIa



IIa

wherein $\text{X} = -\text{C}_2\text{H}_4\text{OC}_2\text{H}_4-$,

(2) reacting a solution of the compound of formula IIa in toluene, *N*-methyl morpholine and methanesulfonyl chloride to obtain the compound of formula IIIa

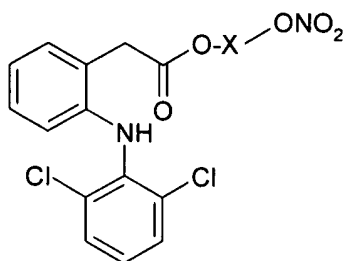


IIIa

wherein X = $-\text{C}_2\text{H}_4\text{OC}_2\text{H}_4-$ and R is $-\text{CH}_3$,

(3) purifying compound IIIa by crystallization; and

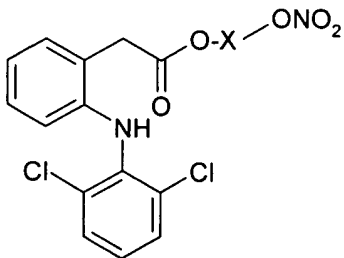
(4) reacting the crystallized compound of formula IIIa with lithium nitrate in N-methyl pyrrolidinone at a temperature of about 75°C to obtain the compound of formula IVa



IVa

wherein X = $-\text{C}_2\text{H}_4\text{OC}_2\text{H}_4-$.

46. (New) A process according to claim 1 for the manufacture of the compound of formula IVb

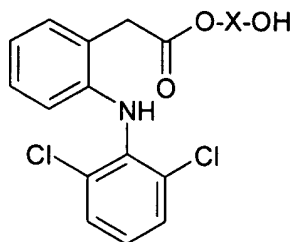


IVb

wherein X = $-\text{C}_4\text{H}_8-$,

comprising:

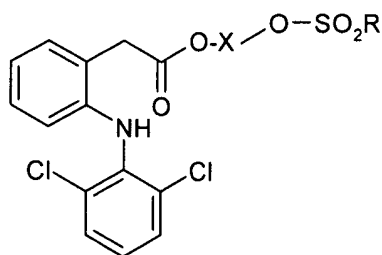
(1) reacting diclofenac with 1,4-butanediol and concentrated sulphuric acid in toluene to obtain the compound of formula IIb



IIb

wherein X = -C₄H₈- ,

(2) reacting a solution of the compound of formula IIb with methanesulfonyl chloride and N-methyl morpholine in toluene to obtain the compound of formula IIIb

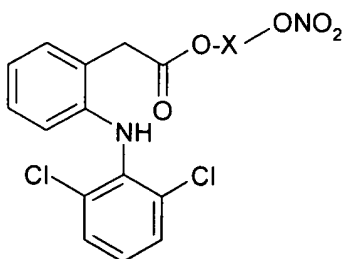


IIIb

wherein X = -C₄H₈- and R is -CH₃ ,

(3) purifying compound IIIb by crystallization; and

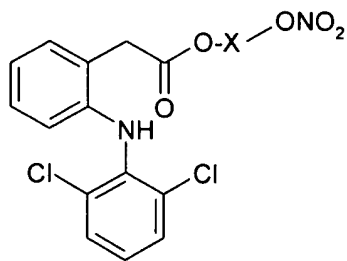
(4) reacting the crystallized compound of formula IIIb with lithium nitrate in N-methyl pyrrolidinone at a temperature of about 70°C to obtain the compound of formula IVb



IVb

wherein X = -C₄H₈- .

47. (New) A process according to claim 1 for the manufacture of the compound of formula IVc

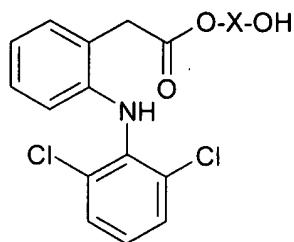


IVc

wherein X = $-\text{C}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4-$,

comprising:

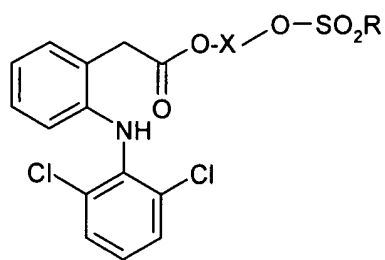
(1) reacting diclofenac with triethylene glycol to obtain the compound of formula IIc



IIc

wherein X = $-\text{C}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4-$,

(2) reacting a solution of compound of formula IIc in toluene with N-methyl morpholine and methanesulfonyl chloride to obtain the compound of formula IIIc

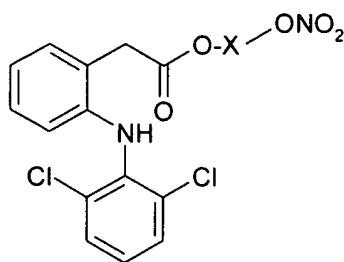


IIIc

wherein X = $-\text{C}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4-$ and R is $-\text{CH}_3$,

(3) purifying compound IIIc by crystallization; and

(4) reacting the purified compound of formula IIIc with sodium nitrate and tetrabutylammonium nitrate in a mixture of n-butylacetate and water at a temperature of about 85°C to obtain the compound of formula IVc



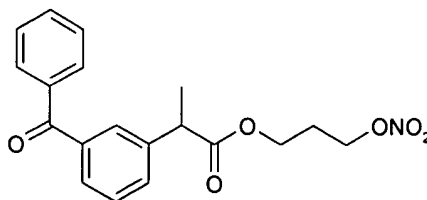
IVc

wherein X = $-\text{C}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4-$

48. (New) A process according to claims 7 or 47, wherein the crystallization process for the compound of formula IVc comprises:

- a) starting from the reaction solution comprising the compound;
- b) evaporating the third solvent;
- c) adding an anti-solvent and/or cooling
- d) isolating the crystals formed, and optionally;
- e) recrystallizing the crystals formed or isolated.

49. (New) A process according to claim 1 for the manufacture of 3-(nitroxy)propyl 2-(2-benzoylphenyl)propanoate of formula IVd

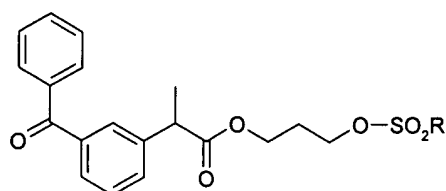


IVd

comprising:

- (1) reacting ketoprofen with 1,3-propanediol to obtain 3-hydroxypropyl-2-(2-benzoylphenyl)propanoate,

(2) reacting 3-hydroxypropyl-2-(2-benzoylphenyl)propanoate in toluene with methanesulfonyl chloride and N-methyl morpholine to obtain 3-[(methylsulfonyl)oxy]propyl-2-(2-benzoylphenyl)propanoate of formula IIIId,

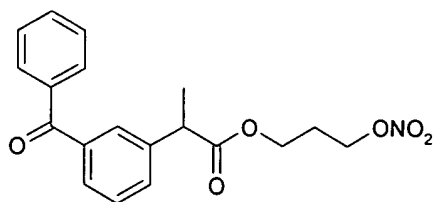


IIIId

wherein R is $-\text{CH}_3$,

(3) purifying compound IIIId; and

(4) reacting the compound of formula IIIId with lithium nitrate in N-methyl pyrrolidinone at a temperature of 70C to obtain 3-(nitroxy)propyl 2-(2-benzoylphenyl)propanoate of formula IVd



IVd